

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS:

- Claim 1. (Withdrawn)
- Claim 2. (Withdrawn)
- Claim 3. (Withdrawn)
- Claim 4. (Withdrawn)
- Claim 5. (Withdrawn)
- Claim 6. (Withdrawn)
- Claim 7. (Withdrawn)
- Claim 8. (Withdrawn)
- Claim 9. (Withdrawn)
- Claim 10. (Withdrawn)
- Claim 11. (Withdrawn)
- Claim 12. (Withdrawn)
- Claim 13. (Withdrawn)
- Claim 14. (Withdrawn)
- Claim 15. (Withdrawn)
- Claim 16. (Withdrawn)
- Claim 17. (Withdrawn)

Claim 18. (Withdrawn)

Claim 19. (Withdrawn)

Claim 20. (Withdrawn)

Claim 21. (Withdrawn)

Claim 22. (Currently Amended) A method of inserting a heterologous gene coding sequence into an endogenous gene in a mouse embryonic stem cell genome and expressing said heterologous gene coding sequence, comprising the step of transforming the mouse embryonic stem cell with a random gene trap vector comprising a DNA construct, wherein the DNA construct (k) lacks a promoter, and (ii) comprises the sequence:

[5' A-P-B-Q-O 3'

in which

P is an internal ribosome entry site (IRES)

Q is the heterologous gene sequence, and

A, B and C are, separately, optional linker sequences;

wherein the DNA construct further comprises a polyadenylation signal at the 3' (downstream) end of Q and a splice acceptor site located 5' (upstream) of Q]

5' X-A-P-B-Q-C-Y 3'

in which

[comprises a splice acceptor sequence;

Y comprises a polyadenylation signal;]

X and Y are separately, DNA sequences substantially homologous with a host gene locus;

P is an internal ribosome entry site (IRES);

Q is the heterologous gene sequence, including a translation start codon; and

A, B, and C are, separately, optional linker sequence[s];

wherein the DNA construct further comprises a polyadenylation signal at the 3' (downstream) end of Q and a splice acceptor site located 5' (upstream) of Q.

Claim 23. (Original) A method according to Claim 22 where the heterologous gene coding sequence is randomly inserted into an endogenous gene so that transcription of the heterologous gene coding sequence is directed by the host regulatory elements of the endogenous gene.

Claim 24. (Original) A method according to Claim 22 in which the splice acceptor permits functional integration of the heterologous gene coding sequence into an intron sequence.

Claim 25. (Canceled)

Claim 26. (Original) A method according to Claim 22 further comprising the step of identifying cells expressing the heterologous gene coding sequence.

Claim 27. (Original) A method according to Claim 26 wherein the heterologous gene coding sequence also codes for a selectable marker and the method comprises selecting cells that express the selectable marker.

Claim 28. (Previously Amended) A mouse embryonic stem cell comprising a heterologous gene code sequence inserted by the method of Claim 22.

Claim 29. (Previously Amended) A descendant of the mouse embryonic stem cell according to Claim 28, wherein the descendant has inherited the inserted heterologous gene coding sequence.

Claim 30. (Withdrawn)

Claim 31. (Withdrawn)

Claim 32. (Currently Amended) A DNA construct for randomly inserting a heterologous gene sequence into a mouse cell genome, said construct lacking a promoter and comprising the sequence:

[5' A-P-B-Q-C 3'

in which

P is an internal ribosome entry site (IRES);

Q is a heterologous gene sequence; and

A, B and C are, separately, optional linker sequences;

wherein the DNA construct further comprises a polyadenylation signal at the 3' (downstream) end of Q and a splice acceptor site located 5' (upstream) of Q]

5' X-A-P-B-Q-C-Y 3'

in which

[comprises a splice acceptor sequence;

Y comprises a polyadenylation signal;]

X and Y are separately, DNA sequences substantially homologous with a

host gene locus;

P is an internal ribosome entry site (IRES);

Q is the heterologous gene sequence, including a translation start codon; and
A, B and C are, separately, optional linker sequence[s];

wherein the DNA construct further comprises a polyadenylation signal at the 3' (downstream) end of Q and a splice acceptor site located 5' (upstream) of Q.

Claim 33. (Original) A DNA construct according to Claim 32 in which the splice acceptor permits functional integration of the heterologous gene into an intron sequence.

Claim 34. (Previously Amended) A DNA construct according to Claim 32 in which the heterologous gene sequence additionally codes for a selectable marker to facilitate selection of mouse cells containing a heterologous gene that has been inserted into an endogenous gene.

Claim 35 (Withdrawn)

Claim 36 (Withdrawn)

Claim 37 (Withdrawn)

Claim 38 (Withdrawn)

Claim 39 (Withdrawn)

Claim 40 (Withdrawn)

Claim 41. (Original) A method according to Claim 22 wherein the heterologous gene coding sequence also codes for antibiotic resistance, and the method comprises selecting cells that express the antibiotic resistance.

Claim 42. (Original) A DNA construct according to Claim 32 wherein the heterologous gene sequence additionally codes for antibiotic resistance.

Claim 43 (Canceled)

Claim 44 (Canceled)

Claim 45 (Canceled)

Claim 46 (Canceled)

Claim 47. (New) A method of inserting a heterologous gene coding sequence into an endogenous gene in a mouse embryonic stem cell genome and expressing said heterologous gene coding sequence, comprising the step of transforming the mouse embryonic stem cell with a random gene trap vector comprising a DNA construct, wherein the DNA construct lacks a promoter, and comprises the sequence:

5' A-P-B-Q-C 3'

in which

P is an internal ribosome entry site (IRES);

Q is the heterologous gene sequence, and

A, B and C are, separately, optional linker sequences;

wherein the DNA construct further comprises a polyadenylation signal at the 3' (downstream) end of Q and a splice acceptor site located 5' (upstream) of Q.

Claim 48. (New) A method according to Claim 47 where the heterologous gene coding sequence is randomly inserted into an endogenous gene so that transcription of the heterologous gene coding sequence is directed by the host regulatory elements of the endogenous gene.

Claim 49. (New) A method according to Claim 47 in which the splice acceptor permits functional integration of the heterologous gene coding sequence into an intron sequence.

Claim 50. (New) A method according to Claim 47 further comprising the step of identifying cells expressing the heterologous gene coding sequence.

Claim 51. (New) A method according to claim 50 wherein the heterologous gene coding sequence also codes for a selectable marker and the method comprises selecting cells that express the selectable marker.

Claim 52. (New) A mouse embryonic stem cell comprising a heterologous gene coding sequence inserted by the method of Claim 47.

Claim 53. (New) A descendant of the mouse embryonic stem cell according to Claim 52, wherein the descendant has inherited the inserted heterologous gene coding sequence.

Claim 54. (New) A mouse comprising a cell according to Claim 53.

Claim 55. (New) A descendant of a mouse according to Claim 54, wherein the descendant has inherited the inserted heterologous gene coding sequence.

Claim 56. (New) A DNA construct comprising the sequence:

5' A-P-B-Q-C 3'

in which

P is an internal ribosome entry site (IRES);

Q is a heterologous gene sequence; and

A, B and C are, separately, optional linker sequences;

wherein the DNA construct further comprises a polyadenylation signal at the 3' (downstream) end of Q and a splice acceptor site located 5' (upstream) of Q.

Claim 57. (New) A DNA construct according to Claim 56 in which the splice acceptor permits functional integration of the heterologous gene into an intron sequence.

Claim 58. (New) A DNA construct according to Claim 56 in which the heterologous gene sequence additionally codes for a selectable marker to facilitate selection of cells containing a heterologous gene that has been inserted into an endogenous gene.

Claim 59. (New) A method according to Claim 47, wherein the heterologous gene coding sequence also codes for antibiotic resistance, and the method comprises selecting cells that express the antibiotic resistance.

Claim 60. (New) A DNA construct according to Claim 56, wherein the heterologous gene sequence additionally codes for antibiotic resistance.